Ovarian excess and the evolution of menopause[1]

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Abstract:

Placental mammals, and especially humans, produce oocytes in a quantity several orders of magnitude larger than the number actually ovulated. There is evidence that this excess is largely an insurance against the ovulation of damaged oocytes and that there is strong selection against damaged oocytes. The selection weakens with age as the pool of undamaged oocytes declines while the number of oocytes that are ovulated remains unchanged. The greater selective importance of earlier reproduction results in low selective pressure to extend the span of reproductive life. In this way we also see how, despite the (variable) aging of individual oocytes, there is not an accumulation of senescence in the germ line over generations. Variation among individuals in their maximum number of oocytes before birth may contribute importantly to variation in the time of menopause several decades later.

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Among animals it is common for there to be a decline and even cessation of reproduction with age. For instance, in female *Drosophila melanogaster* there is a decline in the number of functional ovarioles (Lamb, 1978) and in the rate of egg-laying, which eventually stops. Similar phenomena are common among mammals (Finch and Gosden, 1986), although *Homo* is unusual in having an often long post-reproductive life (Pavelka and Fedigan, 1991). *Pan* approaches *Homo* in this (Caro et al., 1995).

In this paper I will focus on females, because for males the situation is usually fairly well understood and also more straightforward. The other focus is on placental mammals, especially *Homo*; for them the proximate mechanism and evolutionary aspects have each, in different ways, been a source of controversy and even mystery (e.g., Adashi, 1996; Piñón, 2002; Kirkwood, 1998).

Gain

Primordial germ cells of mammals are first detectable as differentiated, oddly, not in the embryo itself (the inner cell mass) but in the endoderm of the yolk sac and the allantois (Ginsburg et al., 1990). At this time they have an average of only 8 mitochondria per cell in *Homo* (Jansen and de Boer, 1998), an extreme bottleneck from which an increase by about four orders of magnitude occurs later. The primordial germ cells migrate, with some (unquantified) loss, into the embryo proper and to the genital

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ridge to form the presumptive gonad. They actively multiply during this migration, in *Mus* having an average of about 7 or 8 mitoses per successful cell lineage (Wassarman and Albertini, 1994), although there is some evidence of appreciable variation among lineages. During their migration one X chromosome is randomly inactivated at the time this happens in somatic cells (Hajkova et al., 2002).

When the primordial germ cells reach the presumptive ovary they are called oogonia. At this stage the X chromosome that had been inactivated earlier loses its suppressors and becomes activated (Monk and McLaren, 1981; Hajkova et al., 2002); what happens in relation to dosage compensation for the newly active X seems still not to have been studied. At about this time also, the cells lose their pre-existing methylation of DNA, including marks of imprinting (Hajkova et al., 2002).

The oogonia are also a kind of stem cell (Lin, 1997) and continue to multiply, producing cells that enter meiosis and are called primary oocytes. The oogonia occur in small clusters, within which they are connected to each other by means of gap junctions (Erickson, 1995). The primary oocytes separate from them by becoming pinched off and then surrounded by a layer of cells called granulosa cells (Gosden et al., 2003). The latter are derived from several ancestral cells (per oocyte) from the degenerating Wolffian duct and mesonephric tubules (Erickson, 1995). The resulting structure is a primordial follicle; it is surrounded by a basement membrane which physically contains it and to some extent isolates it from external influences. The granulosa cells communicate with each other and with the oocyte by gap junctions, through which only rather small molecules are able to pass (Gosden et al., 2003). About 85 percent of the metabolites in an oocyte are derived from its granulosa cells (Erickson, 1995), even before growth, so the granulosa cells (and other follicle cells later) function as nurse cells. The molecular traffic goes in both directions, though, with the oocyte also affecting its surrounding granulosa cells.

The primordial follicles provide the reservoir from which a continuous trickle of follicles start to grow and differentiate toward prospective ovulation. During this differentiation a cavity, the antrum, forms in the follicle and then greatly enlarges; its initiation provides a convenient marker for the stage of follicular development. Some of the specific factors controlling germ-cell and follicle development have been identified (e.g., Amleh and Dean, 2002; Gosden et al., 2003). In *Macaca*, at least, the number of growing follicles is positively related, among individuals and with age, to the number of primordial follicles (Koering, 1983). The same can be inferred for *Homo* from the data of Block (1952).

During follicular growth some genes of the oocyte are imprinted with a mark indicating their maternal origin, sequentially for different genes (Obata and Kono, 2002).

After a newly formed primary oocyte enters meiosis, usually well before birth in most placentals, the initial stages of

prophase 1 take a couple of days to complete even in *Mus*. In all cases the meiotic process is arrested at diplotene by inhibition from the granulosa cells (Adashi, 1996). At this time there are four copies of the genome, each in its own chromatid. The chromatids then lose most of their structure, exposing the DNA in an interphase-like state called dictyotene, with lampbrush chromosomes for active RNA synthesis after the follicle starts to grow. Chiasmata, however, have already been formed and persist. The centrioles are lost in most placentals (but not rodents) and have to be replaced from the fertilizing sperm (Schatten, 1994). This loss ensures that meiosis remains arrested.

The oocytes remain in their arrested phase until well after they start to grow, the rest of prophase 1 not resuming even in *Mus* until the rapid growth of a pre-ovulatory follicle. The arrested phase can therefore last for as long as fifty years in *Homo*.

Mira (1998) has given a good argument that early production of all oocytes is advantageous for monocotous animals like primates because it reduces the probability of poor reproduction. An environmentally caused mutation event then affects only a relatively few oocytes. The advantage is greatly increased if there is selective removal of mutated oocytes, a phenomenon which he argued against but for which there is evidence, discussed below.

Loss

Only a very small proportion of oocytes actually ovulate, escaping from the follicle to enter the Fallopian tube with a chance of possible fertilization. Ovulation doesn't occur before puberty, and all follicles which start to grow before this time degenerate. The number of follicles ovulating per cycle varies among species, the maximum known being about 200 to 800 in *Lagostomus*, a rather large and colonial chinchillid rodent of the Argentine pampas (Weir, 1971). Primates are, on the other hand, characteristically restricted to a single ovulation per cycle, and few mammals have more than ten.

Loss occurs at all stages from primordial germ cells to antral follicles. For oogonia and oocytes in follicles the loss is called atresia and is at least predominantly apoptotic (but cf. te Velde and Pearson, 2002), affecting the entire follicle. Some oogonia are also lost through the ovarian epithelium (Wassarman and Albertini, 1994).

Oogonia don't survive much, if at all, after birth in most placentals, but they have been reported in adults of five genera of lemuriform primates (Butler, 1971) although not in some others (Thibault, 1969), probably in *Ovis* (Cohen, 1977), and occasionally in *Felis* (Baker, 1986). It is unclear whether these persisting oogonia contribute to the functional oocyte pool; there is some evidence against this (Armand Kumar, 1974). Erickson (1966) reported that the maximum number of follicles in *Bos* occurs about 6 months after birth; if correct, this implies the existence of functioning postnatal oogonia.

In *Homo* there are about 6 to 22 antral follicles per cycle during the ages of maximum fertility (Gougeon, 1996). From these one is selected to grow rapidly toward ovulation. The selected follicle appears to be the one most sensitive to follicle-stimulating hormone (FSH), probably because its follicle cells have the most receptors. The selected follicle then synthesizes estradiol, which acts on the hypothalamus to inhibit release of gonadotropin-releasing hormone and thereby secretion of FSH by the pituitary. The consequent reduction of FSH prevents other follicles from being selected (Peters and McNatty, 1980; Erickson, 1995). There also appears to be some direct inhibition by the selected follicle (Armstrong and Webb, 1997). Double ovulation, with the potential for dizygotic twinning and its prenatal problems, is thereby usually prevented. (Nonetheless, 2 to 3 percent of primordial follicles in newborn *Homo* have two oocytes or a binucleated oocyte: Forabosco et al., 1991.)In polycystic ovary syndrome selection of a dominant follicle is impaired, and this in turn impairs the atresia of other follicles (Erickson and Yen, 1993).

Gonadotropin-releasing hormone also, however, suppresses secretion of luteinizing hormone (LH) by the pituitary, and age-related changes in FSH and LH do not coincide. There are, though, also two hormones, called inhibins, that are secreted by the granulosa cells of actively growing follicles. These act directly on the anterior pituitary to inhibit secretion of FSH only. The dominant follicle produces inhibin A, whereas the small antral follicles in the same cohort produce inhibin B. In *Rattus*, transplantation of ovaries from older individuals to younger ones restores normal cyclicity in the ovaries, so deterioration of hypothalamic control with age is indicated here (Burger et al., 2000).

The rate of entry of primordial follicles into the growth phase is somehow regulated to give a rather constant number entering per cycle. This regulation in turn results in a relatively constant amount of estradiol being produced per cycle, with consequent feedback at the proper level for appropriate production of gonadotropin-releasing hormone and thereby FSH (Wood et al., 1994).

Quantitative estimates of the amount and rate of loss of germ cells suffer from a surprising poverty of statistical analysis, especially for *Homo*. The standard figure of a maximum of about 7,000,000 oocytes and oogonia at five months gestation is based on a sample of 2 (Baker, 1963). This paper is also the standard source for numbers at other prenatal ages from two months gestation, at each age with a sample of 2. The lack of closer aging than a month creates an unknown amount of error, as do the histological techniques. Ignoring these and assuming equal relative variation at all ages, a rough calculation gives a standard error of the age-specific means of about 20 percent of the mean. In the paper, however, the estimates are given to five significant figures.

Block (1953) had studied a sample of 7 newborns and reported counts appreciably lower than those of Baker (1963), apparently

from procedural differences. However, Block's sample permits calculation of a coefficient of variation of 34, an unusually high value for a metric character. Age-specific variation in absolute numbers approaches an order of magnitude postnatally also (data of Block, 1952). Data for a sample of 5 newborns studied by Forabosco et al. (1991) give a coefficient of variation of 57. Beaumont and Mandl [1962] studied *Rattus* in a similar way, with 6 to 15 individuals at each age, and their summary statistics permit eleven age-specific coefficients of variation to be calculated. These show no apparent trend with age and have a mean of 59, an even higher value than Block's. (Some unknown part of the variation, in this series and others, is from sampling error in the counts. However, because the mean counts in their Table 5 show a smooth change with age this effect is unlikely to be large.) Similarly high values for *Cavia* can be estimated from a grsph given by Ioannou (1964) and for *Mus* from data of Peters and Levy (1964). Age-specific variation in oocyte number is an important phenomenon which is almost universally neglected.

The above imprecision (as distinct from the variation) is nevertheless not as important as one might expect, because the rate of loss is close to exponential. This means that the instantaneous probability of atresia per average follicle is about constant from the maximum number until near exhaustion. The exponential decline is well documented for several strains of *Mus* (Jones and Krohn, 1961), and it also occurs for *Homo* until about age 40. Around this age the probability of atresia increases until there are nearly no follicles left (Faddy et al., 1992; Faddy and Gosden, 1996; a well-known purported critique by Leidy et al. [1998] overlooked the latter paper and adds nothing substantive.) Menopause occurs when the follicle number reaches, very roughly, 10 (Richardson and Nelson, 1990), but effective sterility occurs several years before this. (The commonly cited value of about 1000 for the number of oocytes at menopause is based on an incorrect model given by Faddy et al., 1992, the revised 1996 version simply repeating the same value.)

In *Rattus* the decline is exponential until relatively old age, but then the proportional rate decreases rather than increases (Hirshfield, 1991). *Cavia* has a more extreme situation, in which there is an apparently constant number of follicles after about i month *post partum*, lasting through the last count at 12 months (Ioannou, 1964). This general pattern is unexplained but could in principle result from surviving and functioning oogonia, which have not, however, been reported.

For several species there are data which permit rough estimates (Table 1) of the absolute rate of loss. The cited references give the data; the estimates are from my own calculations.

How much of this variation is real is unclear because of large differences in methods of estimation, but the methods were constant within specific studies and so their differences probably have little effect on the estimates. It is impossible to calculate meaningful error estimates for the values in the table.

Table 1. Probability of atresia of a random follicle per day

Mus, strains A and RIII (Jones & Krohn, 1961)	6×10^{-3}
Mus, strain CBA (Jones & Krohn, 1961)	2×10^{-2}
Rattus (Mandl & Shelton, 1959; Beaumont & Mandl, 1964)	5×10^{-3}
Cavia, until constancy (Ioannou, 1964)	3×10^{-2}
Homo, until final acceleration (various)	5×10^{-4}
Bos (Erickson, 1966)	6×10^{-4}

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Estradiol and inhibin A don't decrease with age until quite close to menopause. However, inhibin B does decrease, as the number of follicles recruited to the growth cohort decreases. This decrease in inhibin B permits FSH to increase in the late 30s. The increase in FSH then stimulates a greater proportion of the remaining primordial follicles to enter the growth phase (Klein et al., 1996b; Burger et al., 1998), causing a positive feedback that accelerates the decline in follicle number found from that time. An earlier slow increase in FSH may also affect the process. The secretion of inhibin B, or a threshold of the pituitary's responsiveness to it, may vary over time somewhat randomly, resulting in the increased variation of cycle length that occurs until menopause (Treloar, 1974). There is nevertheless an unexplained apparent delay of several years from the start of accelerated loss of follicles around the late 30s until the start of more variable cycling around the early 40s.

Secretion of FSH increases somewhat in the early-middle follicular phase of the cycle starting as early as the late 20s (Ahmed-Ebbiary et al., 1994, whose unusually large sample permitted detection of this small effect.) A small increase in LH was also detected in the late 30s; the mid-follicular increase of FSH in the late 30s is not reflected in the parts of the cycle when inhibin is secreted (Lee et al., 1988). These effects may result from an age-increased sensitivity of the pituitary to gonadotropin-releasing hormone. The higher level of FSH increases the rate of growth of follicles and thereby leads to the small decrease in mean cycle length until perimenopause (Klein et al., 1996a; Treloar, 1974).

When the number of antral follicles is reduced to a level at which there are sometimes none available, at the appropriate time of the cycle, to grow towards ovulation, anovulartory cycles start to occur. Such a lack may also explain rare earlier anovulatory cycles (te Velde and Pearson, 2002.)

It is well known that there is a moderate amount of variation among women as to the time of their menopause. The report of a large prospective study (Treloar, 1981) includes a graph from which a standard deviation of 3.2 years can be calculated for those individuals who had not used supplemental estrogen; the commonly cited earlier report of the same study (Treloar, 1974) is incomplete. Retrospective studies, such as that of Goodman et al. (1978) on four populations in Hawaii, tend to have values a little higher. They also have not separated out users of supplemental

estrogen, which Treloar found to increase the variation as well as the mean.

A rather similar amount of variation appears to occur for earlier stages of reproductive decline that are less easy to identify at the individual level, such as the age at effective sterility ("oopause") and the age at which acceleration of atresia occurs (te Velde et al., 1998b). Treloar (1981) gave data on the moderately ambiguous age of onset of increasingly variable cycles; these give a standard deviation of 3.6 years. A separate set of Treloar's data imply a standard deviation of only 2.1 years for the interval from then until menopause.

There also appears to be a good correlation (but not yet quantified) among women with respect to these post-pubertal stages, so that an early occurrence of one is a fairly good predictor of an early menopause (te Velde et al., 1998b). Age at menarche, however, is quite uncorrelated with age at menopause (Treloar, 1974) and is causally distinct. Despite being affected a bit by various environmental factors, age at menopause has a rather high heritability and is polygenic (Cramer et al., 1995; Torgerson et al., 1997; Snieder et al., 1998; Treloar et al., 1998; te Velde et al., 1998a).

The mean age at menopause is similar among different societies, including the classical Mediterranean (Amundsen and Diers, 1970), but there is some adverse effect of poor living conditions, perhaps especially poor nutrition (Gray, 1976; Yen and Lein, 1984; Gosden, 1985; Tarim et al., 1985; Pavelka and Fedigan, 1991; Leidy, 1994). Low life expectancy at birth in some societies is sometimes used to support unimportance of life after menopause there, but high mortality in childhood negates the argument. For instance, about 28 percent of women in seventeenth-century Europe lived at least to menopause (Yen and Lein, 1984).

With about 39 years between mean menarche and mean menopause, it is sometimes stated that there are about 470 potential ovulations. This ignores the occurrence of anovulatory cycles after menarche and before menopause, as well as those from such events as pregnancy and lactation. Considering the variation in the latter events, but not the use of anovulatory contraceptive pills, there is variation among societies from perhaps 160 to 350 mean lifetime ovulations (Eaton et al., 1994).

In human populations with no apparent contraception, mean female fecundity is maximal at about 25 years and then has a convex-up to linear decline on an arithmetic scale; absolute rates differ among populations (Ellison, 1996).

Theory

Why is there such a vast excess of oocytes? And why does menopause occur? It seems likely that an answer to the former question will help to explain the latter.

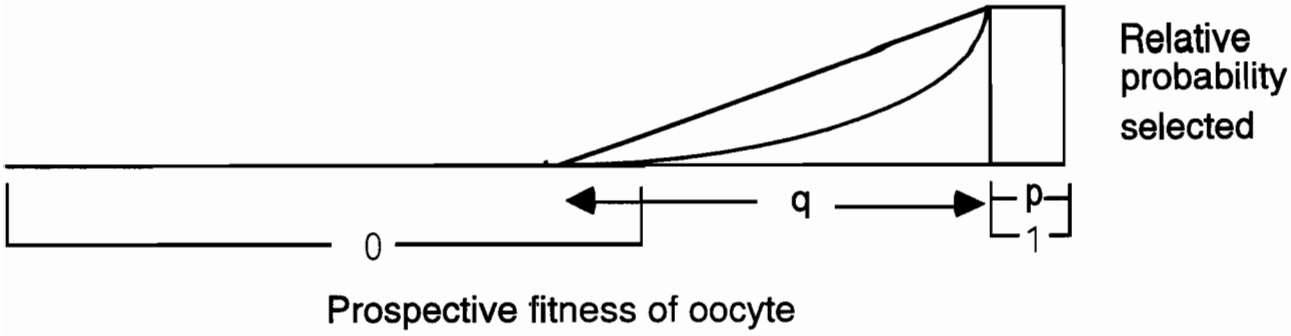

Figure 1. Probability of ovulation in relation to prospective fitness of oocyte. See text.

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Oocytes are known to vary in their immediate and prospective fitness, as discussed in the next section The distribution of these fitnesses is mostly unknown, but a simple model (Figure 1) should be adequate to provide the basic structure of the distribution. Some proportion p' of the available oocytes at a particular time will have a fitness of about 1. The remainder, $q' = 1 - p'$, will have lower fitness. (A scaling factor converts p' to $p = rp'$ and q' to $q = rq'$.) There will in addition be oocytes which are irrevocably destined for atresia because of defects. They have fitness 0 and can mostly be excluded from consideration with respect to those follicles selected for ovulation. However, there are also some oocytes with prospective fitness 0 which do have a chance of being selected for ovulation, as shown by death of zygotes and embryos.

In the simplest case, the probability of selection changes linearly over the range of q, i.e. each probability of selection in this range corresponds to the same number of oocytes or, equivalently, follicles. Then the probability of an optimal oocyte being selected is $p/(p + 0.5q)$. If more than one is selected, the probability that all n are optimal decreases to $(p/(p + 0.5q))^n$. For instance, if there are twice as many selectable but suboptimal oocytes as optimal ones, then the probability of an optimal one being selected is 0.5 and the probability that both of two selected are optimal is 0.25.

Over time, p will become smaller relative to q. This is partly a result of the greater probability of prospectively fitter oocytes being removed from the pool by selection. In addition, the pool of primordial follicles progressively deteriorates in quality as a result of the accumulation of damage with age.

It is important to distinguish three stages in the selection of follicles. The central one is the selection of a cohort of primordial follicles to grow toward ovulation. This decreases p by hypothetically removing a fitter set of follicles from the pool of primordial follicles. Selection also undoubtedly occurs among primordial follicles irrespective of such cohort removal. Such selection increases p by removing less fit follicles. Becaus the growth cohort is already removed from the pool of primordial follicles, selection from it of the one or more follicles to grow rapidly to ovulation has no further effect on the pool. It is, though, of course very important in ensuring a viable ovulated egg.

More realistically, the probability of selection in the q interval is concave up, so that oocytes of lower fitness have a lower probability of selection than in the linear case. This is represented by the curved line in Figure 1. A simple function corresponding to this case is the power function, $y = x^v$. Here y is the relative probability of being selected and x is the proportional distance in the q interval from its left end. The exponent v represents the stringency of selection. A larger exponent results in a smaller area under the curve and thereby a greater probability of an optimal oocyte being selected. The pool of optimal oocytes will obviously decrease more rapidly in such a case, a situation which becomes important when and if the pool of available follicles becomes limited.

The term 'relative probability' above refers to the fact that some proportion of follicles are apparently lost randomly, without respect to their prospective fitness. For instance, the great majority of follicles are lost before menarche or the equivalent. Probably almost all of these would be lost under the model above if they were to survive into the reproductive part of the female's life, but many of them start to grow (an irreversible process: Goodman et al., 1979; Hirshfield, 1996) during the pre-reproductive period, when there is no chance whatever of ovulation. The unknown proportion of follicles that are lost randomly has no effect on the model, but it is relevant to the large number of follicles that are produced. Probably pre-reproductive cycling is important physiologically in preparation for the initiation of ovulation and reproduction. However, a large proportion of genuinely random losses would reduce the impact of selective processes, the basis of the present theory, on the problem of ovarian excess. The theory predicts that such random loss is relatively minor.

For those species in which oogonia survive into the adult stage and remain functional, the distribution of prospective fitnesses of oocytes remaining at a particular time is likely to be modified. Probably a newly produced oocyte will have an expected prospective fitness greater than that of the currently available oocyte pool. This will slow (and possibly, if quite improbably, even reverse) the decrease of p relative to q with age.

Early reproduction is always more valuable selectively than later reproduction, ceteris paribus, because there is a non-zero probability of death at all ages. In addition, in species (like all placental mammals) with overlapping generations, earlier reproduction gives a surprisingly large advantage in terms of more generations per unit time (Cole, 1954). These effects are integrated as the sensitivity of overall fitness to age-specific variation in its components (Charlesworth, 1994). And the decreasing sensitivity with age during adult life is what permits the evolution of senescence. In turn, physiological senescence feeds back on age-specific fitness and gives a third causal path for decline of fitness with age. There is nevertheless wide variation among species in the rate of this decline.

As Wood et al. (1994) explicitly note, the regulation of ovarian function to an optimal state in the earlier part of

reproductive life leads to deleterious consequences later, eventually resulting in menopause.

A higher probability of selecting an optimal follicle to grow towards ovulation requires more stringent criteria of selection. This, however, depletes the pool of available follicles more rapidly. The effects of the depletion can be reduced by having a larger initial pool of available follicles, but the effects are not eliminated. There is therefore a tradeoff between efficiency of selection and how long successful reproduction can continue. A single offspring per pregnancy, as with primates, makes it particularly important for ovulations to be of good-quality oocytes, because abortion will commonly eliminate at least one cycle of potential reproduction entirely.

Evidence

There are several kinds of evidence that the decline in oocyte numbers with age is important. In *Homo*, before about age 30 the number of primordial (resting) follicles is reduced primarily by direct atresia, but later most of the reduction comes to occur by follicles being recruited to enter the growth phase (Gougeon, 1996). The scope for selective removal is thereby reduced, contributing to the increase in poorly fit oocytes that are ovulated. Possibly the change is related to a lower degree of inhibition to growth by the smaller numbers of follicles themselves. There is a similar shift in *Mus* (Gougeon, 1996). The number of small antral follicles at the start of a cycle in *Homo* declines with age and seems to be correlated with the number of remaining primordial follicles (Scheffer et al., 1999).

Oocytes which have been unable to reach diplotene are eliminated at a particular age; this age varies among species (Baker, 1986.)

Survivors of childhood cancer have usually experienced treatment with severely cytotoxic drugs, which most strongly affect dividing cells such as those of the ovaries. Larson et al. (2003) found that such survivors have only about half the usual number of small antral follicles, reflecting the diminished reserve. However, the number of large antral follicles was normal. This means that the criteria for atresia of the smaller follicles were relaxed so that fertility would not be impaired at that time. As a tradeoff, the ages at which reduction of fertility and menopause occur are younger because of the smaller pool of follicles (Freeman et al., 2000). Similar results occur for other cytotoxicants, even including destruction of oocytes by metabolites of cigarette smoke (Hirschfield and Flaws, 2000).

Shorter menstrual cycles in *Homo* are correlated with earlier menopause, perhaps in relation to the concentration of FSH (te Velde et al., 1998a), which increases around age 40. The absolute number of follicles lost per unit time is, unsurprisingly, lowest in late reproductive life of *Homo* (Leidy Sievert, 2001); there is a large but continuous drop around age 40 in the mean number of follicles available to be chosen for rapid pre-ovulatory growth (Gougeon, 1998), the drop being from about 12 to 3.5. The increase

in probability of a follicle entering atresia after about age 40 probably reflects both the depletion of good follicles and the increase of FSH lowering the threshold for recruitment of a follicle to the growth phase.

There is evidence from a number of species that removal of one ovary causes the other to double in size (because of having more large follicles) and ovulate at twice the rate for a single ovary when both are present (Weir and Rowlands, 1977; Guraya, 1985). The size of the pool of resting follicles is reduced more rapidly and the number of growing follicles per ovary is thereby increased, but oocyte depletion and atresia occur at the normal rate per follicle thereafter. There is thereby again a relaxation of the criteria for atresia. In hemiovariectomized *Rattus* nearly all available follicles are recruited in order to get the appropriate number for ovulation (Hirshfield, 1982; Meredith et al., 1992). Even in *Mus* removal of one ovary results in appreciably earlier infertility (Adams, 1970; Eichenlaub-Ritter et al., 1988), although in most strains lower fertility with age is not (under normal conditions) a result of exhaustion of oocytes (Jones and Krohn, 1961). Nevertheless, in both *Rattus* and *Mus*, older individuals have relatively few follicles and atresia is reduced to maintain the ovulation quota (Hirshfield, 1991). Lower-quality embryos are thereby produced.

From the other end, artificial selection for a larger litter size in *Mus* increased the ovulation rate by increasing the number of follicles permitted to start growth; the proportion of suitable later-stage follicles permitted to start rapid growth toward ovulation was unchanged (Sparrow et al., 1979).

Irregular menstrual cycles in *Homo*, which increase after about age 40, appear ordinarily to be due to a temporary lack of growing follicles at about the appropriate stage (Richardson et al., 1987; Gougeon et al., 1994; O'Connor, 1998). This effect of follicular depletion becomes important when there are a few thousand follicles per ovary (Richardson et al., 1987) and accelerates thereafter.

The two largest species for which data are available, *Bos* and *Homo*, have ostensibly the slowest rates of loss of follicles, with rodentsbeing one or even two orders of magnitude faster. This pattern marches with the much greater longevity of the larger species, but it is perhaps unexpected because of their smaller litter sizes and therefore the greater importance of each zygote. The pattern suggests that long-lived species are to some extent able to retard the deterioration of their oocytes with age. How this might be done is unclear, but its absence in rodents suggests that it has a nontrivial cost.

Quality of oocytes as well as their number deteriorates greatly with age. Most of the decline in fecundity of *Homo* with age comes from an increase in early abortions (O'Connor, 1998; Holman et al., 2000), as is the case for other placentals (Adams, 1970). Holman and Wood (2001) found a loss of 96 percent in *Homo*. That this is a result of decline in oocyte quality is shown by its relation to the ages of the donor and recipient in assisted reproduction: the age of the recipient has little effect, whereas

with both embryo transfer (van Kooij et al., 1996) and oocyte transfer (Kornafel and Sauer, 1994; Yaron et al., 1995; te Velde et al., 1998a) the age of the donor is very important. Deterioration of oocyte quality with age has been shown also in several other species by similar reciprocal transplants (Adams, 1970), although oocytes from older individuals of *Mus* remain good (Jones, 1979) except for very old individuals (Adams, 1970).

One might think that oocyte chromosomes, at least, should show little deterioration with age, because they remain in an arrested state until actively growing toward ovulation, and this view was once common. In *Homo*, though, more than half of even the successfully ovulated oocytes after age 40, and even a quarter of embryos, have gross chromosomal abnormalities (Hassold et al., 1993; Volarcik et al., 1998; Magli et al., 1998; Eichenlaub-Ritter, 1998). These are mostly trisomies, but monosomies should have a similar frequency because of the symmetry of nondisjunction unless they are preferentially shunted into polar bodies. Monosomies are presumably even less viable than trisomies, except for X monosomy. And almost all of the detectable aneuploid oocytes degenerate without being chosen for ovulation (Guraya, 1999).

In the CBA strain (now subdivided) of *Mus*, which, unlike other strains but like *Homo*, does exhaust its oocytes, there is also an increase of aneuploidy with age, as oocyte exhaustion approaches and the scope for choice becomes less (Brook et al., 1984; Eichenlaub-Ritter et al., 1988). Removal of one ovary in *Mus* and *Homo* results in a later increase in aneuploidy of ovulated oocytes (Eichenlaub-Ritter et al., 2000), again presumably because of lower selectivity for these oocytes chosen for ovulation. There are now genetically engineered strains of *Mus* with unusually high and low maximum numbers of oocytes (Hirshfield and Flaws, 2000). However, any results that may come from these strains will have to be interpreted in light of known concomitant defects in controlling molecules such as the apoptosis-regulator caspase.

Many degenerating oocytes are still in the zygotene or pachytene stages of meiosis 1, so perhaps crossing-over results in abnormalities (Byskov, 1982). In addition, more oocytes from older individuals have abnormalities in the spindle microtubules, in *Homo* this occurring in most follicles from older individuals (Klein et al., 1996a). According to Volarcik et al. (1998), resumption of the first meiotic division is the age-relevant stage in nondisjunction. The oocyte cytoplasm and granulosa cells deteriorate with age and affect what happens at meiotic resumption.

Even more than the nuclear genome, mitochondria deteriorate with age. Unlike the case for most somatic cells, almost all of the 100,000 or so mitochondria in a large oocyte have only a single copy of its genome. This may even be the case in a continuous germ line from generation to generation (Jansen and de Boer, 1998). Although haploidy permits more effective intracellular selection against defective mitochondria, large numbers of defects do accumulate. Furthermore, clonal expansion of mutated mitochondria is common in most cells, including oocytes, and may be a predominant factor (Kraytsberg et al., 2003; Khrapko et al., 2003).

Rearrangements in mitochondrial DNA have been found in half or more oocytes and multiple deletions in about 80 percent (Barritt et al., 1999; Hsieh et al., 2002). Only the deletions show a large increase with age (Suganuma et al., 1993). At least partly from these defects, oxidizing radicals and anions increase with age and antioxidants decrease, putting proteins, DNA, and microtubules at risk. This increase is probably accelerated during oocyte growth because of the greater oxydizing metabolism then (Dorland et al., 1998). It is plausible that mitochondrial deterioration is causally involved in the increase of nondisjunction with age (Schon et al., 2000).

That accumulation of mitochondrial defects actually causes deterioration of oocyte quality with age has been shown for *Homo* by injecting mitochondria from young oocytes into older ones (Cohen et al., 1998). This resulted in improved viability of embryos derived from the older oocytes. Perez et al. (2000) injected mitochondria from granulosa cells into apparently antral oocytes of *Mus* and found an appreciable reduction in subsequent atresia. In both these experiments there were many more indigenous mitochondria than injected ones, showing a rescue effect by the latter.

A common mitochondrial deletion in *Homo* is said to occur more often in oocytes from primordial follicles than in embryos of unstated age (Perez et al., 2000); when the apparent selection takes place is unknown and there was no mention of possibly confounding factors such as relative age.

Discussion

Selection is an imperfect process, yet it is the only way for fitness to increase. Adaptations deteriorate as the world changes, and this applies to cells as well as to species, in different ways. Even oocytes senesce. Obviously, though, germ-cell senescence can't be cumulative over generations; cells of a baby really are inherently younger than those of its doting grandmother.

This lack of cumulative senescence is caused partly by selection on embryos. Many are inviable and abort, and in some mammals this is what determines litter size. Thus the hundreds of ovulated oocytes of *Lagostomus* result in a usual litter size of only 2, the others being unfertilized or eliminated at the 2-cell stage (Rowlands and Weir, 1984).

Zygotic selection isn't enough, however. The very large majority of oocytes are defective, and with random ovulation and fertilization there would still be cumulative deterioration over generations. An important paper by Krakauer and Mira (1999) shows that among diverse animals the proportion of germ cells undergoing atresia varies just as would be expected by strong selection among oocytes. Animals with little atresia, as well as (to a lesser extent) those with many offspring, have an appreciably higher minimum number of mitochondria during the formation of oocytes. Having only 8 to 20 mitochondria per cell at the mitochondrial bottleneck, genetic variation among the oocytes of placental mammals is potentially large. We don't know how strong

the selection among oocytes actually is, but the lack of cumulative deterioration over generations indicates that it is strong enough.

The other component of a rejuvenated zygote is the sprem. Spermatocytes Also senesce, and most sperm of mammals are chromosomally defective. (They lack mitochondrial DNA, possibly at least in part because of the further potential for damage it would cause.) There is a very large potential for selection among sperm during their passage through the female reproductive tract, and commonly only one actually reaches the egg. Oddly, such selection hasn't been studied, so far as I know, since a promising and underappreciated paper by Bateman (1960; also Braden, 1958) on *Mus*. The usual occurrence of a normal zygote despite the great predominance of damaged sperm indicates, however, that it is strong.

And menopause? With selection among follicles (plus their senescence, and whatever random atresia occurs) depleting the pool of available oocytes, selection becomes weaker with age, and the proportion of defective oocytes that ovulate increases. There is such a large excess of oocytes because there must be enough of a reserve pool for selection to be able to give a sufficiently high age-specific probability of a good oocyte being ovulated.

A greater initial number of oocytes would give a pool of oocytes that lasts a little longer, but because the loss is at an exponential rate even a doubling of the initial pool would extend reproductive life by only about four years. Presumably the selective value of a slightly longer period of reproduction is offset by the several kinds of cost of such an increase.

The large but poorly known variation among individuals in their maximum number of oocytes may well, however, contribute to the variation among individuals in the time of their menopause. (Nothing is known about variation among individuals in rate of atresia and its degree of selectivity, or in the postulated fuzzy threshold in the estrogen-gonadotropin feedback loop.) The variation in time of menopause looks sufficiently small in itself to suggest some sort of selective regulation, but the perspective of the present paper suggests that the underlying causal variation is, on the contrary, so large as to be only weakly constraining.

There are other possibilities of selective advantage for human menopause. Shanley and Kirkwood (2001) have modeled two of them and found that their joint effect may be sufficient even though neither is individually. One is the benefit to the infant of having hir mother survive until hse is able to function independently in society. The other advantage is the care that grandmothers[1] can and do give to their grandchildren, which they would be less able to do if they could still bear children of their own.

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[1]In this context one may contemplate the finding (Allman, 1999) that males live as .long as females in primate species where fathers care for their offspring directly.

These are both real effects and undoubtedly contribute to the unusual life history of *Homo*, but their relevance is to the length of life after menopause rather than to the time of menopause itself. I think that in a broader context these effects and others are secondary to the apparently unpreventable deterioration of oocytes with age and to the reduced adaptive importance of reproduction by older individuals.

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